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Baseline Neurodegeneration Influences the Longitudinal Effects of Tau on Cognition

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Abstract.
Background: Cerebrospinal fluid t-tau (CSF t-tau) is a measure of neurodegeneration in Alzheimer's disease (AD) and has been increasingly demonstrated to be a non-specific biomarker within the AD continuum.
Objective: We sought to test whether t-tau influences the longitudinal effects of amyloid-β (Aβ) and phospho-tau (p-tau) on memory and executive function (EF) in mild cognitive impairment (MCI).
Methods: 319 MCI individuals from the Alzheimer's Disease Neuroimaging Initiative (ADNI) with baseline and 2-year CSF Aβ, p-tau, t-tau, and neuropsychological assessments were studied. Mediation and moderation analyses evaluated the role of t-tau in the effects of Aβ and p-tau on memory and EF over 2 years.
Results: We found that high baseline p-tau but not Aβ was associated with higher t-tau and lower memory scores at 2 years follow-up. The association between p-tau and memory impairment was partially mediated by t-tau, whereby higher p-tau was indirectly associated with lower memory via higher t-tau. t-tau also moderated the association between p-tau and memory. When t-tau level was relatively lower, higher p-tau was associated with lower memory scores at 2 years. When t-tau level was higher, the memory scores were low regardless of the p-tau level.
Conclusion: Tau-induced neurodegeneration is one key pathway by which AD pathology (p-tau) affects memory impairment. Furthermore, in individuals with lower levels of tau-induced neurodegeneration, higher levels of p-tau were required for memory impairment. Our findings suggest that t-tau plays a significant role in how early AD pathology affects cognitive outcomes.

Keywords: Alzheimer's disease, biomarkers, cerebrospinal fluid, cognitive dysfunction, executive function, memory, mild cognitive impairment

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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INTRODUCTION

Alzheimer's disease (AD) pathophysiology is postulated to follow a temporal evolution, beginning with amyloid-β (Aβ) plaques and tau neurofibrillary tangles (NFTs) followed by tau-induced neuronal dysfunction as the eventual pathway leading to cognitive impairment [1, 2]. While this sequential progression has been widely studied [2, 3], the role of neurodegeneration burden on the effects of Aβ and tau leading to cognitive dysfunction in the early stage of AD remains unclear. In this regard, tau-induced neural dysfunction can be caused not only by Aβ and NFTs, but also by non-AD pathologies during the aging process, such as oxidative stress [4–6]. Therefore, most elderly individuals will have some burden of neurodegeneration when the sequel of AD pathophysiology takes place. As it remains unclear how tau-induced neurodegeneration modifies the toxic effects of Aβ and tau on cognitive dysfunction, studies evaluating the role of tau-induced neurodegeneration burden on the impact of Aβ and tau on cognition are of paramount importance so as to support a more precise application of disease-modifying drugs in AD [7].

Cerebrospinal fluid (CSF) $A\beta_{1\text{-}42}$, phospho-tau (p-tau), and total-tau (t-tau) are biomarkers of Aβ, NFTs, and neurodegeneration, respectively, and have been incorporated in the recently proposed A/T/(N) classification [8, 9]. However, the different modalities of the AT(N) measurements are not interchangeable [10] and abnormalities in CSF Aβ (measures of brain Aβ deposition) and t-tau (measures of neurodegeneration) have been shown to occur at least 15 years before expected symptom onset and precede their corresponding neuroimaging biomarkers of Aβ (amyloid PET) and neurodegeneration ([^{18}F]flurodeoxyglucose PET and MRI) [1, 11]. Therefore, CSF is a valuable biomarker of AD that is able to evaluate early changes of the burden of Aβ, NFTs, and neurodegeneration in the mild cognitive impairment (MCI) stage of AD.

While studies show that low CSF $A\beta_{1\text{-}42}$, high p-tau, and high t-tau levels correlate with poor global cognitive performance [12] and a high CSF p-tau/$A\beta_{42}$ ratio predicted worsening cognitive impairment on global cognition and episodic memory in AD [13], the influence of t-tau on the effects of Aβ and p-tau on cognition in MCI remains unknown. Therefore, we sought to identify how t-tau influences the role of Aβ and p-tau on memory and executive function (EF) over a 2-year period, which is a typical time frame for a clinical trial design in a cohort of individuals with MCI, given that early intervention in prodromal dementia may offer the greatest chance of treatment success in improving clinical outcomes.

METHODS

Database description and study participants

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

In this study, we selected 319 MCI individuals who underwent lumbar puncture and neuropsychological assessments at baseline and 2-year follow-up. We defined MCI as those with a Mini-Mental State Examination (MMSE) score ≥ 24, Clinical Dementia Rating (CDR) 0.5, subjective and objective memory loss, having normal activities of daily living, and absence of any neuropsychiatric diseases such as depression, and dementia [14]. The inclusion/exclusion criteria adopted by ADNI can be found at http://www.adni-info.org.

Standard protocol approvals, registrations, and patient consents

The ADNI study was approved by the Institutional Review Boards of all of the participating institutions. Informed written consent was obtained from all participants at each site.

CSF analysis

CSF $A\beta_{1\text{-}42}$, CSF p-tau_{181p}, and CSF t-tau were measured using the Luminex multiplex platform (Luminex, Austin, TX, USA) and Innogenetics INNO-BIA AlzBio3 (Innogenetics, Ghent, Belgium) immunoassay reagents. The CSF biomarker data set used in this study were obtained from the ADNI file 'UPENNBIOMK_MASTER.csv' and analyzed based on the updated recommendations from ADNI. The details of the ADNI methods for the acquisition and measurement of CSF can be found at http://www.adni-info.org. Lower CSF $A\beta_{1\text{-}42}$ levels

reflects increased Aβ burden, higher CSF p-tau levels reflects increased tau burden and higher CSF t-tau levels reflects increased neuronal degeneration burden [15].

Neuropsychological assessments

The neuropsychological assessments were performed by certified raters using standardized ADNI protocols. The CDR, ADNI-mem, and ADNI-EF data sets used in this study were obtained from the ADNI files 'CDR.csv' and 'UWNPSYCHSUM_01_28_15-5.csv' respectively. ADNI-mem and ADNI-EF are validated composite memory and EF scores derived using data from the ADNI neuropsychological battery [16, 17]. Briefly, a modern psychometric approach was used to analyze the Rey Auditory Verbal Learning Test, AD assessment schedule-cognition, MMSE and Logical Memory tests to obtain a composite memory score. Similarly, category fluency—animals, category fluency—vegetables, trails A and B, digit span backwards, WAIS-R digit symbol substitution and 5 clock drawing items (circle, symbol, numbers, hands, time) were analyzed to obtain a composite EF score. Lower ADNI-mem and ADNI-EF scores reflect poorer memory and EF performance respectively. Both the ADNI-mem and ADNI-EF were shown to be useful composite measures of memory and EF in MCI, as good as or better than its composite parts [16, 17]. Therefore, both the ADNI-mem and ADNI-EF were chosen as the measures of cognitive outcomes in this study. The details of the ADNI protocols for the neuropsychological assessments and methods for developing ADNI-mem and ADNI-EF can be found at http://www.adni-info.org.

Statistical methods

The analytical sample included 319 individuals who provided data on all variables of interest at baseline (Table 1). This sample size was sufficient for our analysis [18]. Focal measures were CSF $A\beta_{1\text{-}42}$, CSF p-tau_{181p}, CSF t-tau, ADNI-mem, and ADNI-EF. Data on the first two came from the baseline (Time 1; T1), and those on the latter three came from the baseline and the 2-year follow-up (Time 2; T2). Covariates included age, gender, education, and *APOE* ε4 status at baseline.

Using Mplus version 7.4, we performed mediation analysis with two waves of data to illustrate temporal causations [19, 20]. Mediation analysis falls within the overarching framework of structural equation modelling (SEM) [21]. The variance of Aβ, p-tau, t-tau, ADNI-mem, and ADNI-EF differed substantially. Substantial difference in variance across the variables may lead to improper solutions in SEM, for example: estimated absolute correlation > 1.0 [21]. We therefore used standardized scores (z scores) on Aβ, p-tau, t-tau, ADNI-mem, and ADNI-EF in the analysis. Robust standard error was employed to address non-normality. Missing data was handled by full information maximum likelihood. A model is regarded to fit with the data when the χ^2 value is not significant. However, as the χ^2 value is sensitive to sample size, it should not be emphasized [21]. Instead, we referred to Comparative Fit Index (CFI), Tucker Lewis Index (TLI), Root Mean Square Error of Approximation (RMSEA), and Standardized Root Mean Square Residual (SRMR). As a rule of thumb, CFI and TLI values of > 0.90, and RMSEA and SRMR values of < 0.10 suggest an acceptable model fit [22].

Figure 1A illustrated our conceptual model of the interplay among Aβ, p-tau, and t-tau on ADNI-mem and ADNI-EF. Figure 1B illustrated the corresponding statistical model. Covariates (e.g., gender), concurrent covariances (e.g., T2 ADNI-mem with T2 ADNI-EF), and autoregressive effects (e.g., effect of T1 t-tau on T2 t-tau) were controlled for. Central to our research objectives, T2 t-tau was regressed on T1 Aβ and T1 p-tau. T2 ADNI-mem and T2 ADNI-EF were regressed on T1 Aβ, T1 p-tau, and T1 t-tau. These associations were relevant to the mediating

Table 1
Baseline demographics and sample variables

Variables	N	M (S.D.) or %
Age, mean, y (S.D.)	319	72.81 (7.33)
Males, n (%)	319	187 (58.60)
Education, mean, y (S.D.)	319	16.25 (2.61)
MMSE, mean (SD)	319	27.70 (1.81)
APOE ε4 carriers, *n* (%)	319	165 (51.7)
T1 ADNI MEM, mean (S.D.)	319	0.23 (0.63)
T1 ADNI EF, mean (S.D)	319	0.32 (0.82)
T1 CSF $A\beta_{1\text{-}42}$	319	171.15 (54.15)
T1 CSF p-tau_{181p}	319	39.30 (23.34)
T1 CSF t-tau	319	90.05 (52.24)
T2 ADNI MEM, mean (S.D.)	318	0.16 (0.84)
T2 ADNI EF, mean (S.D)	315	0.25 (1.00)
T2 CSF t-tau	236	95.67 (57.46)

Percentage (%) is reported for males and *APOE* ε4 carriers. Mean (M) and (S.D.) are reported otherwise. Aβ, amyloid-β ADNI EF, ADNI executive function composite score; ADNI MEM, ADNI memory composite score; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; N, sample size; p-tau, phosphorylated tau; t-tau, total tau; T1, baseline; T2, 2-year follow-up.

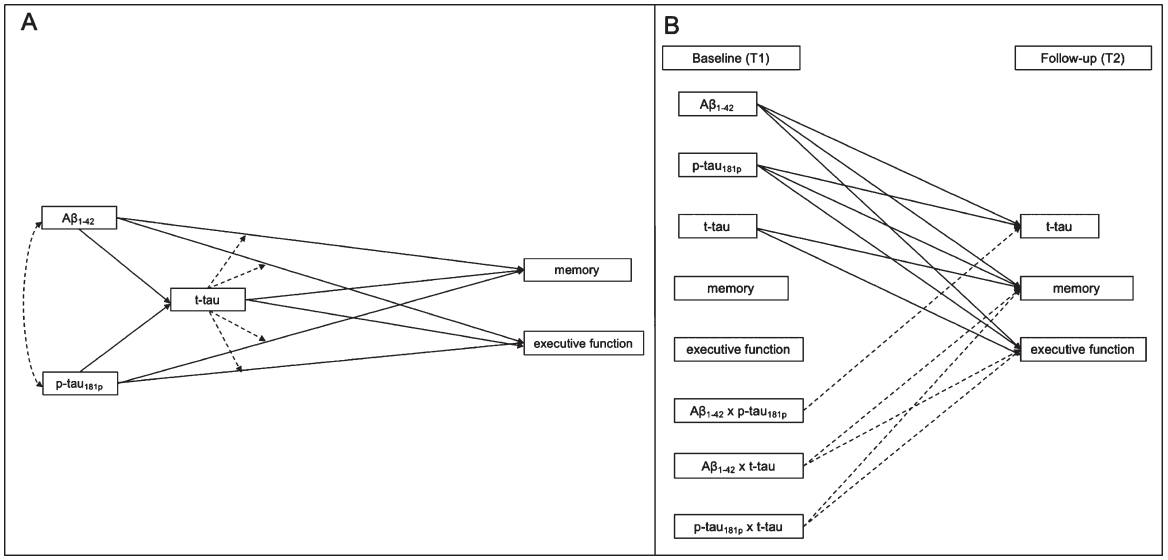

Fig. 1. Proposed framework of $A\beta_{1\text{-}42}$, p-tau_{181p}, and t-tau interplay on memory and executive function. A) Conceptual model of the interplay among $A\beta_{1\text{-}42}$, p-tau_{181p}, and t-tau on memory and executive function at 2 years. Dotted lines indicate interaction effects. B) Statistical model of the interplay among $A\beta_{1\text{-}42}$, p-tau_{181p}, and t-tau on memory and executive function at 2 years. Dotted lines indicate interaction effects. Covariates, concurrent covariances, and autoregressive effects were controlled for but are not shown.

role of t-tau in the association of Aβ and p-tau with memory and EF.

Mediating effect or indirect effect is concerned with whether the effect of an antecedent on an outcome is channeled through by the third variable – mediator. Quantitatively, it refers to the product term of the coefficient of the relation between antecedent (e.g., Aβ) and mediator (t-tau), and that of the relation between mediator (t-tau) and outcome (e.g., ADNI-mem) [23]. When these two coefficients were significant, we came up with the indirect effect. The assumption of a normal distribution of indirect effect is often violated. One way of evaluating the statistical significance of an indirect effect is to calculate its 95% confidence interval (CI_{95}) using bootstrapping. An indirect effect is deemed significant when its CI_{95} excludes zero. However, bootstrapping is not possible against robust standard error. Hence, we utilized a R-based online tool that adopts Monte Carlo method [24] to calculate CI_{95}.

Moderating effect is also known as interaction effect. A significant moderating effect means that the strength and/or direction of the relationship between predictor and outcome varies across levels of the third variable – moderator [23]. Regarding the moderating role of t-tau, we regressed T2 ADNI-mem and T2 ADNI-EF on the interaction effect between T1 Aβ and T1 t-tau, and that between T1 p-tau and T1 t-tau. To provide a comprehensive picture of the interplay among Aβ, p-tau, and t-tau, we also addressed the interaction effect between Aβ and p-tau on t-tau. Specifically, we regressed T2 t-tau on the interaction effect between T1 Aβ and T1 p-tau. Significant interaction effect was followed up by simple slope analysis [25].

RESULTS

Baseline demographics, *APOE* ε4, CSF AD biomarkers, and cognitive performance of the study cohort are summarized in Table 1. The proposed model of the interplay among $A\beta_{1\text{-}42}$, p-tau_{181p}, and t-tau on ADNI-mem and ADNI-EF fitted the data well: χ^2 (8) = 23.44, $p = 0.003$, CFI = 0.987, TLI = 938, RMSEA = 0.078, and SRMR = 0.012 (Fig. 2).

We found that high baseline (T1) p-tau, but not low Aβ, was associated with higher t-tau at 2-year follow-up (T2) (path coefficient [b] = 0.11, $p = 0.007$). High T1 p-tau, but not low Aβ, was also associated with lower T2 ADNI-mem scores ($b = –0.07$, $p = 0.044$). Both T1 p-tau and Aβ were not associated with T2 ADNI-EF scores.

We further demonstrated that high T1 t-tau was associated with lower T2 ADNI-mem scores ($b = –0.10$, $p = 0.019$). The product term of the coefficient of the p-tau – t-tau relation and that of the t-tau – ADNI-mem relation was significant (indirect effect = -0.012, CI_{95} –0.027, –0.001). Together,

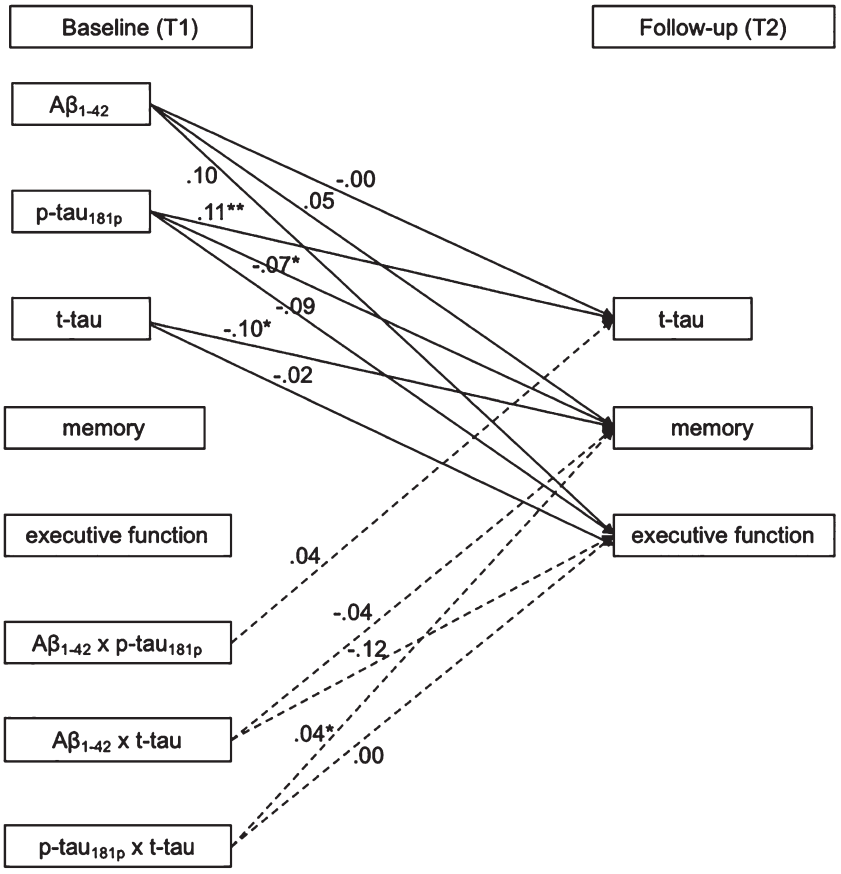

Fig. 2. The interplay among $A\beta_{1\text{-}42}$, p-tau_{181p}, and t-tau on memory and executive function at 2 years. Findings of the interplay among $A\beta_{1\text{-}42}$, p-tau_{181p}, and t-tau on memory and executive function at 2 years. Dotted lines indicate interaction effects. Covariates, concurrent covariances, and autoregressive effects were controlled for but are not shown. Numbers reported are path coefficients. The residual variance of T2 t-tau, T2 memory, and T2 EF were 0.13, 0.24, and 0.36 respectively. $^{*}p < 0.05$, $^{**}p < 0.01$.

these findings suggest that t-tau partially mediated the effect of p-tau on ADNI-mem at 2-year follow-up.

There was a significant interaction effect between T1 p-tau and T1 t-tau on T2 ADNI-mem ($b = 0.04$, $p = 0.012$), indicating that baseline t-tau also moderated the effect of p-tau on ADNI-mem at 2 years. As illustrated in Fig. 3, when baseline t-tau level was relatively lower (1SD below mean), higher p-tau was associated with lower ADNI-mem score at 2 years ($b = –0.11$, $p = 0.012$). When baseline t-tau level was higher (1 SD above mean), the ADNI-mem score was low regardless of the p-tau level ($b = –0.03$, $p = 0.340$).

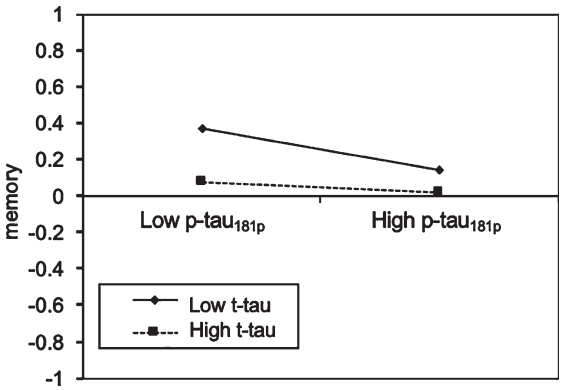

Fig. 3. CSF t-tau mediates and moderates the effect of tau on memory performance at 2 years. Interaction effect between T1 p-tau_{181p} and T1 t-tau on T2 memory.

DISCUSSION

In the present study, we found that p-tau is associated with lower memory scores at 2 years, and that one mechanism for this association may be due to an increased tau-induced neurodegeneration. We further found that baseline t-tau moderated how p-tau was

associated with cognitive outcomes. Specifically, we found that in individuals with low t-tau burden, higher p-tau was associated with lower memory scores over 2 years. Comparatively, in individuals with greater t-tau burden, the memory performance was poorer regardless of p-tau.

While Aβ plaques and NFTs are the main pathological markers of AD, it is postulated that Aβ accumulation is insufficient to cause cognitive deterioration directly [26], whereas phospho-tau which occurs downstream of Aβ, is more closely related to cognitive decline [27]. Indeed, emerging evidence suggests that the burden of NFTs is consistently associated with severity of cognitive impairment, Aβ is less associated with cognition [27, 28]. An AD clinicopathological review shows that neocortical NFTs density best correlates with ante-mortem cognitive status whereas the correlation is less strong for neuritic and diffuse Aβ plaques [29]. Similarly, a neuropathological study shows that NFTs, but not Aβ load, predict cognitive status in AD [30] while another study shows that NFTs mediate the association of Aβ and cognitive decline [31]. Recent *in vivo* studies using tau PET tracers also show that the spatial accumulation of tau is associated with domain-specific cognitive impairment in AD [32, 33]. In MCI or mild AD patients, the association of cognitive impairment was stronger with inferior temporal [^{18}F]T807 uptake than with cortical [^{11}C]PIB uptake [32]. Also, NFTs and tau PET uptake in the medial temporal lobe correlate with memory impairment but not other cognitive domains [34]. Therefore, our findings of higher burden of p-tau, but not Aβ, being linked to memory impairment at 2 years further support the current literature that a close relationship exists between NFTs and cognitive performance in AD.

Neurodegeneration is widely associated with cognitive impairment in dementia and is closely linked to tau NFTs [30]. In this regard, the loss of microtubule stabilizing function and the toxic effects of NFTs contribute to disturbances in the normal structural and regulatory functions of the cytoskeleton. This compromises axonal transport which leads to synaptic dysfunction and neurodegeneration [35]. A recent study shows that the relationship between p-tau and cognitive deficits in AD is weakly related to Aβ, but are in part mediated by grey matter volume loss [27]. Hypometabolism, a correlate of synaptic function, has also been shown to act as a mediator between p-tau and subsequent cognitive impairment [36, 37]. In our study, we extend these findings by showing that t-tau partially mediates the effect of p-tau on memory impairment in MCI using longitudinal CSF and neuropsychological assessments at baseline and 2 years, suggesting that p-tau leads to memory impairment partly through t-tau. Given the central role of p-tau pathology in neurodegeneration [38], our results may support potential p-tau targeted interventions to prevent neurodegeneration and subsequent memory impairment.

We further found that t-tau moderates the effect of p-tau on memory impairment in MCI. Specifically, memory performance is impaired when the burden of t-tau is high regardless of the level of p-tau pathology, suggesting that once the extent of neurodegeneration crosses a certain threshold, p-tau may no longer have a significant impact on memory performance. This is consistent with a previous neuropathological study showing that the density of neocortical synapses correlates strongly with cognitive performance [39]. On the other hand, higher p-tau pathology is associated with lower memory scores at year 2 when the burden of t-tau is low, which suggest that the impact of p-tau on memory performance is greater when t-tau is below a certain threshold. In addition, these findings suggest that p-tau may lead to memory impairment through mechanisms other than t-tau related neurodegeneration in the early stages of the AD continuum. The mechanisms of neurodegeneration other than tau-induced neurodegeneration include cerebrovascular disease and neuroinflammation among others. Indeed, a recent study evaluating the role of tau underlying cognitive impairments in subcortical vascular cognitive impairment (SVCI) reports that cerebral small vessel disease is associated with increased tau uptake in inferior temporal regions [40]. Phosphor-tau accumulation in the inferior and medial temporal region also correlates with worse cognition, suggesting that p-tau may represent a final common pathway for patients with SVCI. In another study that examined the associations between CSF neuroinflammation biomarkers and cerebrovascular disease with AD pathology, CSF p-tau and t-tau are linked to high levels of CSF YKL-40, ICAM-1 and VCAM-1 in cognitively unimpaired elderly, MCI and AD dementia individuals [41]. Therefore, future investigations assessing the interactions of cerebrovascular disease and neuroinflammation on tau and cognition in MCI will be warranted to further clarify the mechanisms of p-tau and cognitive performance prior to the onset of neurodegeneration.

The main strength of the present study is the inclusion of MCI individuals from the ADNI cohort with

well characterized baseline and 2-year follow-up CSF data. In ADNI, CSF is processed using standardized methods and the quality control enables reliable measurements of longitudinal changes in CSF AD biomarkers.

There are limitations in our study. Firstly, we based our study on the hypothesis that AD biomarkers become abnormal in a temporally ordered manner, with Aβ and CSF p-tau as upstream followed by CSF t-tau and cognitive impairment as downstream effects [1, 2, 9]. While this present hypothetical framework is widely accepted, other less Aβ-centric pathways have been proposed. For example, cognitively normal persons with neuronal injury biomarker abnormalities and normal Aβ levels are shown to be indistinguishable from those with abnormal Aβ levels on imaging markers, clinical features and cardiovascular risk factors [42], suggesting that AD-related neuronal injury may be independent from Aβ [43]. Also, studies using task-free functional MRI to investigate the relationship between synaptic activity and AD found that network disturbances may occur prior to amyloid biomarkers becoming abnormal in AD at-risk individuals [44, 45]. In this regard, the lack of healthy controls as a comparison group in our study may also limit the interpretation of the findings observed in MCI as a distinct process from anormal aging. Secondly, our model aims to study the interplay between core AD biomarkers (Aβ, p-tau, and t-tau) and cognition. Emerging evidence has reported the concomitant presence of other pathophysiologies such as cerebrovascular disease, TDP-43 inclusions, and neuroinflammation in AD that may contribute substantially to clinical disease expression [40, 41, 46]. Therefore, future studies focusing on the interplay between AD pathophysiology should evaluate the contributions of these pathophysiologies that have been linked to AD. Lastly, there may be a selection bias within the ADNI study population. The highly specialized pool of subjects from the ADNI and the relatively small sample size of our study limit the generalizability of our findings. Therefore, our findings will need to be confirmed in another larger independent study cohort.

In summary, our study demonstrates a dynamic relationship between CSF t-tau and the effects of p-tau on memory in MCI. Importantly, we show that p-tau contribute to memory impairment even when the burden of t-tau is low. These findings suggest that CSF t-tau levels play a significant role in how early AD pathology affects cognitive outcomes.

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Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/20-1425r1).

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